

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61K 9/00</b>	<b>A1</b>	(11) International Publication Number: <b>WO 99/16417</b>
		(43) International Publication Date: <u>8 April 1999 (08.04.99)</u>

(21) International Application Number: <b>PCT/US97/17899</b>	(22) International Filing Date: <u>1 October 1997 (01.10.97)</u>	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(71) Applicant (for all designated States except US): FLEMINGTON PHARMACEUTICAL CORPORATION [US/US]; 43 Emery Avenue, Flemington, NJ 08822 (US).	(72) Inventor; and (75) Inventor/Applicant (for US only): DUGGER, Harry, A., III [US/US]; 548 Sargentville Road, Flemington, NJ 08822 (US).	<b>Published</b> With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.
(74) Agent: BEHR, Omri, M.; 325 Pierson Avenue, Edison, NJ 08837 (US).		

**(54) Title:** BUCCAL, POLAR AND NON-POLAR SPRAY OR CAPSULE**(57) Abstract**

Buccal aerosol sprays or capsule using polar and non-polar solvent have now been developed which provide biologically active compounds for rapid absorption through the oral mucosa, resulting in fast onset of effect. The buccal polar compositions of the invention comprises formulation (I): aqueous polar solvent 30-99.89 %, active compound 0.001-60 %, optionally containing flavoring agent 0.1-10 %. The non-polar composition of the invention comprises formulation (II): non-polar solvent 20-85 %, active compound 0.005-50 %, and optionally flavoring agent 0.1-10 % and propellant 50-80 %.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IR	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

TITLE OF THE INVENTION

## BUCCAL, POLAR AND NON-POLAR SPRAY OR CAPSULE

BACKGROUND OF THE INVENTION

5 It is known that certain biologically active compounds are better absorbed through the oral mucosa than through other routes of administration, such as through the stomach or intestine. However, formulations suitable for such administration by these latter routes present their own problems. For example, the biologically active compound must

10 be compatible with the other components of the composition such as propellants, solvents, etc. Many such formulations have been proposed. For example, U.S.P. 4,689,233, Dvorsky *et al.*, describes a soft gelatin capsule for the administration of the anti-coronary drug nifedipine dissolved in a mixture of polyether alcohols. U.S.P. 4,755,389, Jones *et al.*,

15 describes a hard gelatin chewable capsule containing nifedipine. A chewable gelatin capsule containing a solution or dispersion of a drug is described in U.S.P. 4,935,243, Borkan *et al.* U.S.P. 4,919,919, Aouda *et al.*, and U.S.P. 5,370,862, Klokkers-Bethke, describe a nitroglycerin spray for administration to the oral mucosa comprising nitroglycerin, ethanol, and

20 other components. An orally administered pump spray is described by Cholcha in U.S.P. 5,186,925. Aerosol compositions containing a hydrocarbon propellant and a drug for administration to a mucosal surface are described in U.K. 2,082,457, Su, U.S.P. 3,155,574, Silson *et al.*, U.S.P. 5,011,678, Wang *et al.*, and by Parnell in U.S.P. 5,128,132. It

25 should be noted that these references discuss bioavailability of solutions by inhalation rather than through the membranes to which they are administered.

SUMMARY OF THE INVENTION

A buccal aerosol spray or soft bite gelatin capsule using a polar or non-polar solvent has now been developed which provides biologically active compounds for rapid absorption through the oral mucosa, resulting 5 in fast onset of effect.

The buccal aerosol spray compositions of the present invention, for transmucosal administration of a pharmacologically active compound soluble in a pharmacologically acceptable non-polar solvent comprising in weight % 10 of total composition: pharmaceutically acceptable propellant 5-80%, non-polar solvent 20-85%, active compound 0.05-50%, suitably additionally comprising, by weight of total composition a flavoring agent 0.01-10%. Preferably the composition comprises: propellant 10-85%, non-polar solvent 25-89.9%, active compound 0.01-40%, flavoring agent 1-8%; most 15 suitably propellant 20-70%, non-polar solvent 30-74.75%, active compound 0.25-35%, flavoring agent 2-7.5%.

The buccal polar spray compositions of the present invention, for transmucosal administration of a pharmacologically active compound soluble 20 in a pharmacologically acceptable polar solvent comprising in weight% of total composition: polar solvent 30-99.69%, active compound 0.001-60%, suitably additionally comprising, by weight of total composition a flavoring agent 0.1-10%. Preferably the composition comprises: polar solvent 37-98.58%, active compound 0.005-55%, flavoring agent 0.5-8%; most 25 suitably polar solvent 60.9-97.06%, active compound 0.01-40%, flavoring agent 0.75-7.5%.

The soft bit gelatin capsules of the present invention for transmucosal administration of a pharmacologically active compound, at 30 least partially soluble in a pharmacologically acceptable non-polar solvent, having charged thereto a fill composition comprising in weight % of total

composition: non-polar solvent 4-99.99%, emulsifier 0-20%, active compound 0.01-80%, provided that said fill composition contains less than 10% of water, suitably additionally comprising, by weight of the composition: flavoring agent 0.01-10%. Preferably, the soft bite gelatin 5 capsule comprises: non-polar solvent 21.5-99.975%, emulsifier 0-15%, active compound 0.025-70%, flavoring agent 1-8%; most suitably: non-polar solvent 28.5-97.9%, emulsifier 0-10%, active compound 0.1-65.0%, flavoring agent 2-6%.

10 The soft bite polar gelatin capsules of the present invention for transmucosal administration of a pharmacologically active compound, at least partially soluble in a pharmacologically acceptable polar solvent, having charged thereto a composition comprising in weight % of total composition: polar solvent 25-99.89%, emulsifier 0-20%, active compound 0.01-65%, 15 provided that said composition contains less than 10% of water, suitably additionally comprising, by weight of the composition: flavoring agent 01-10%. Preferably, the soft bite gelatin capsule comprises: polar solvent 37-99.95%, emulsifier 0-15%, active compound 0.025-55%, flavoring agent 1-8%; most suitably: polar solvent 44-96.925%, emulsifier 0-10%, 20 active compound 0.075-50%, flavoring agent 2-6%.

The buccal pump spray composition of the present invention for transmucosal administration of a pharmacologically active compound where said active compound is soluble in a pharmacologically acceptable non-polar 25 solvent said composition comprise in weight % of total composition: non-polar solvent 30-99.69%, active compound 0.005-55%, flavoring agent 0.1-10%.

It is an object of the invention to coat the mucosal membranes either 30 with extremely fine pleats of spray containing the active compounds or a solution or paste thereof from bite capsules.

It is also an object of the invention to administer to a mammalian in need of same preferably man, a predetermined amount of a biologically active compound by this method or from a soft gelatin bite capsule.

5 A further object is a sealed aerosol spray container containing a composition of the non polar spray formulation, and a metered valve suitable for releasing from said container a predetermined amount of said composition.

10 As the propellant evaporates after activation of the aerosol valve, a mist of fine droplets is formed which contains solvent and active compound.

The propellant is a non-Freon material, preferably a C<sub>3-8</sub> hydrocarbon of a linear or branched configuration. The propellant should be substantially 15 non-aqueous. The propellant produces a pressure in the aerosol container such that under expected normal usage it will produce sufficient pressure to expel the solvent from the container when the valve is activated but not excessive pressure such as to damage the container or valve seals.

20 The non-polar solvent is a non-polar hydrocarbon, preferably a C<sub>7-18</sub> hydrocarbon of a linear or branched configuration, fatty acid esters, and triglycerides, such as miglyol. The solvent must dissolve the active compound and be miscible with the propellant, i.e., solvent and propellant must form a single phase at 0-40°C at a pressure range of 1-3 atm.

25

The non-polar aerosol spray compositions of the invention are intended to be administered from a sealed, pressurized container. Unlike a pump spray, which allows the entry of air into the container after activation, the aerosol container of the invention is sealed at the time of 30 manufacture. The contents of the container are released by activation of a metered valve, which does not allow entry of atmospheric gasses with each

activation. Such containers are commercially available.

A further object is a pump spray container containing a composition of the spray formulation, and a metered valve suitable for releasing from 5 said container a predetermined amount of said composition.

A further object is a soft gelatin bite capsule containing a composition of as set forth above. The formulation may be in the form of a viscous solution or paste containing the active compounds. Although solutions are 10 preferred, paste fills may also be used where the active compound is not soluble or only partially soluble in the solvent of choice. Where water is used to form part of the paste composition, it should not exceed 10% thereof. (All percentages herein are by weight unless otherwise indicated.)

15 The polar or non-polar solvent is chosen such that it is compatible with the gelatin shell and the active compound. The solvent preferably dissolves the active compound. However, other components wherein the active compound is not soluble or only slightly soluble may be used and will form a paste fill.

20

Soft gelatin capsules are well known in the art. See, for example, U.S.P. 4,935,243, Borkan et al., which is incorporated herein by reference for its teaching of such capsules. The capsules of the present invention are intended to be bitten into to release the low viscosity solution or paste 25 therein, which will then coat the buccal mucosa with the active compounds. Typical capsules, which are swallowed whole or bitten and then swallowed, deliver the active compounds to the stomach, which results in significant lag time before maximum blood levels can be achieved or subject the compound to a large first pass effect. Because of the enhanced absorption of the 30 compounds through the oral mucosa and no chance of a first pass effect, use of the bite capsules of the invention will eliminate much of the lag time,

resulting in hastened onset of biological effect. The shell of a soft gelatin capsule of the invention may comprise, for example: gelatine 50-75%, glycerine 20-30%, colorants 0.5-1.5%, water 5-10%, and sorbitol 2-10%.

5 The active compound may include biologically active peptides, central nervous system active amines, sulfonyl ureas, antibiotics, antifungals, antivirals, sleep inducers, antiasthmatics, bronchial dilators, antiemetics, histamine H-2 receptor antagonists, barbiturates, prostaglandins and neutraceuticals.

10

The active compounds may also include antihistamines, alkaloids, hormones, benzodiazepines and narcotic analgesics. While not limited thereto, these active compounds are particularly suitable for non-polar pump spray formulation and application.

15

#### BRIEF DESCRIPTION OF THE DRAWING

The figure is a schematic diagram showing routes of absorption and processing of pharmacologically active substances in a mammalian system.

20

#### DESCRIPTION OF THE PREFERRED EMBODIMENTS

The preferred active compounds of the present invention are in anionized, salt form or as the free base of the pharmaceutically acceptable salts thereof (provided, for the aerosol or spray compositions, they are soluble in the spray solvent). These compounds are soluble in the non-polar

25 solvents of the invention at useful concentrations or can be prepared as pastes at useful concentrations. These concentrations may be less than the standard accepted dose for these compounds since there is enhanced absorption of the compounds through the oral mucosa. This aspect of the invention is especially important when there is a large (40-99.99%) First

30 pass effect.

As propellants for the non polar sprays, propane, N-butane, iso-butane, N-pentane, iso-pentane, and neo-pentane, and mixtures thereof may be used. N-butane and iso-butane, as single gases, are the preferred propellants. It is permissible for the propellant to have a water content of 5 no more than 0.2%, typically 0.1-0.2%. (All percentages herein are by weight unless otherwise indicated.) It is also preferable that the propellant be synthetically produced to minimize the presence of contaminants which are harmful to the active compounds. These contaminants include oxidizing agents, reducing agents, Lewis acids or bases, and water. The concentration of each of these should be less than 0.1%, except that water 10 may be as high as 0.2%.

Suitable non-polar solvents for the capsules and the non-polar sprays include (C<sub>2</sub>-C<sub>24</sub>) fatty acid C<sub>2</sub>-C<sub>8</sub> esters, C<sub>7</sub>-C<sub>18</sub> hydrocarbon, C<sub>2</sub>-C<sub>8</sub> alkanoyl 15 esters, and the triglycerides of the corresponding acids. When the capsule fill is a paste, other liquid components may be used instead of the above low molecular weight solvents. These include soya oil, corn oil, other vegetable oils.

20 As solvents for the polar capsules or sprays there may be used low molecular weight polyethyleneglycols (PEG) of 400-1000 Mw (preferably 400-600), low molecular weight (C<sub>2</sub>-C<sub>8</sub>) mono-and polyols and alcohols of C<sub>7</sub>-C<sub>18</sub> linear or branch chain hydrocarbons, glycerin may also be present and water may also be used in the sprays, but only in limited amount in the 25 capsules.

It is expected that some glycerin and water used to make the gelatin shell will migrate from the shell to the fill during the curing of the shell. Likewise, there may be some migration of components from the fill to the 30 shell during curing and even throughout the shelf-life of the capsule. Therefore, the values given herein are for the compositions as prepared, it

being within the scope of the invention that minor variations will occur.

The preferred flavoring agents are synthetic or natural oil of peppermint, oil of spearmint, citrus oil, fruit flavors, sweeteners (sugars, 5 aspartame, saccharin, etc.), and combinations thereof.

The active substances include the active compounds selected from the group consisting of cyclosporine, sermorelin, Octreotide acetate, calcitonin-salmon, insulin lispro, sumatriptan succinate, clozepine, cyclo-10 benzaprine, dexfenfluramine hydrochloride, glyburide, zidovudine, erythromycin, ciprofloxacin, ondansetron hydrochloride, dimenhydrinate, cimetidine hydrochloride, famotidine, phenytoin sodium, phenytoin, carboprost thrombamine, carboprost, carnitine, valerian, echinacea, diphenhydramine hydrochloride, isoproterenol hydrochloride, terbutaline sulfate, terbutaline, 15 theophylline, albuterol sulfate, and the like.

The formulations of the present invention comprise an active compound or a pharmaceutically acceptable salt thereof. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically 20 acceptable non-toxic acids or bases including organic and inorganic acids or bases.

When an active compound of the present invention is acidic, salts may be prepared from pharmaceutically acceptable non-toxic bases. Salts 25 derived from all stable forms of inorganic bases include aluminum, ammonium, calcium, copper, iron, lithium, magnesium, manganese, potassium, sodium, zinc, etc. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of 30 primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion-

exchange resins such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethyl-piperidine, glucamine, glucosamine, histidine, isopropylamine, lysine, methylglucosamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purine, theobromine, triethylamine, trimethylamine, tripropylamine, etc.

When an active compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids. Such acids 10 include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, etc. Particularly preferred are citric, hydrobromic, maleic, phosphoric, sulfuric, 15 and tartaric acids.

In the discussion of methods of treatment herein, reference to the active compounds is meant to also include the pharmaceutically acceptable salts thereof. While certain formulations are set forth herein, the actual 20 amounts to be administered to the mammal or man in need of same are to be determined by the treating physician.

The invention is further defined by reference to the following examples, which are intended to be illustrative and not limiting.

- 10 -

**NOT FURNISHED UPON FILING**

- 11 -

**NOT FURNISHED UPON FILING**

F. Octreotide acetate (Sandostatin<sup>®</sup>) lingual spray

	Amounts	preferred amount	most preferred amount
octreotide acetate	0.001-0.5	0.005-0.250	0.01-0.10
acetic acid	1-10	2-8	4-6
5 sodium acetate	1-10	2-8	4-6
sodium chloride	3-30	5-25	15-20
flavors	0.1-5	0.5-.4	2-3
ethanol	5-30	7.5-20	9.5-15
water	15-95	35-90	65-85
10 flavors	0.1-5	1-4	2-3

G. Calcitonin-salmon lingual spray

	Amounts	preferred amount	most preferred amount
Calcitonin-salmon	0.001-5	0.005-2	.01-1.5
15 ethanol	2-15	3-10	7-9.5
water	30-95	50-90	60-80
Polyethylene glycol	2-15	3-10	7-9.5
sodium chloride	2.5-20	5-15	10-12.5
flavors	0.1-5	1-4	2-3

20

H. insulin lispro, lingual spray

	Amounts	preferred amount	most preferred amount
insulin,	20-60	4-55	5-50
glycerin,	0.1-10	0.25-5	0.1-1.5
25 dibasic sodium phosphate,	1-15	2.5-10	4-8
m-cresol,	1-25	5-25	7.5-12.5
zinc oxide	0.01-0.25	.05-0.15	0.075-0.10
m-cresol,	0.1-1	0.2-0.8	0.4-0.6
phenol	trace amounts	trace amounts	trace amounts
30 ethanol	5-20	7.5-15	9-12
water	30-90	40-80	50-75
propylene glycol	5-20	7.5-15	9-12
flavors	0.1-5	0.5-3	0.75-2

adjust pH to 7.0-7.8 with HCl or NaOH

## EXAMPLE 2

**CNS active amines and their salts: including but not limited to tricyclic amines, GABA analogues, thiazides, phenothiazine derivatives, Serotonin antagonists and serotonin reuptake inhibitors**

5        A.     Sumatriptan succinate lingual spray

		Amounts	preferred amount	most preferred amount
	sumatriptan succinate	0.5-30	1-20	10-15
	ethanol	5-60	7.5-50	10-20
	propylene glycol	5-30	7.5-20	10-15
10	polyethylene glycol	0-60	30-45	35-40
	water	5-30	7.5-20	10-15
	flavors	0.1-5	1-4	2-3

B.     Sumatriptan succinate bite capsule

		Amounts	preferred amount	most preferred amount
	sumatriptan succinate	0.01-5	0.05-3.5	0.075-1.75
	polyethylene glycol	25-70	30-60	35-50
	glycerin	25-70	30-60	35-50
	flavors	0.1-10	1-8	3-6

20

C.     Clozepine lingual spray

		Amounts	preferred amount	most preferred amount
	Clozepine	0.5-30	1-20	10-15
	ethanol	5-60	7.5-50	10-20
25	propylene glycol	5-30	7.5-20	10-15
	polyethylene glycol	0-60	30-45	35-40
	water	5-30	7.5-20	10-15
	flavors	0.1-5	1-4	2-3

D. Clozepine Non-Polar lingual spray with propellant

	Amounts	preferred amount	most preferred amount
Clozepine	0.5-30	1-20	10-15
Miglyol	20-85	25-70	30-40
5 Butane	15-80	30-75	60-70
flavors	0.1-5	1-4	2-3

E. Clozepine Non-Polar lingual spray without propellant

	Amounts	preferred amount	most preferred amount
10 Clozepine	0.5-30	1-20	10-15
Miglyol	70-99.5	80-99	85-90
flavors	0.1-5	1-4	2-3

F. Cyclobenzaprine Non polar lingual spray

	Amounts	preferred amount	most preferred amount
Cyclobenzaprine (base)	0.5-30	1-20	10-15
Miglyol	20-85	25-70	30-40
Iso-butane	15-80	30-75	60-70
20 flavors	0.1-5	1-4	2-3

G. dexfenfluramine hydrochloride lingual spray

	Amounts	preferred amount	most preferred amount
25 dexfenfluramine Hcl	5-30	7.5-20	10-15
ethanol	5-60	7.5-50	10-20
propylene glycol	5-30	7.5-20	10-15
polyethylene glycol	0-60	30-45	35-40
water	5-30	7.5-20	10-15
30 flavors	0.1-5	1-4	2-3

**EXAMPLE 3**  
**Sulfonylureas**

**A. Glyburide lingual spray**

	Amounts	preferred amount	most preferred amount
5 Glyburide	0.25-25	0.5-20	0.75-15
ethanol	5-60	7.5-50	10-20
propylene glycol	5-30	7.5-20	10-15
polyethylene glycol	0-60	30-45	35-40
water	2.5-30	5-20	6-15
10 flavors	0.1-5	1-4	2-3

**B. Glyburide non-polar bite capsule**

	Amounts	preferred amount	most preferred amount
Glyburide	0.01-10	0.025-7.5	0.1-4
15 olive oil	30-60	35-55	30-50
polyoxyethyl- ated oleic glycerides	30-60	35-55	30-50
flavors	0.1-5	1-4	2-3

**20 EXAMPLE 4**

**Antibiotics anti-fungals and anti-virals**

**A. zidovudine (formerly called azidothymidine (AZT) (Retrovir) non-polar lingual spray**

	Amounts	preferred amount	most preferred amount
25 zidovudine	10-50	15-40	25-35
Soya oil	20-85	25-70	30-40
Butane	15-80	30-75	60-70
flavors	0.1-5	1-4	2-3

B. Erythromycin bite capsule bite capsule

		Amounts	preferred amount	most preferred amount
	Erythromycin	25-65	30-50	35-45
	polyoxyethylene glycol	5-70	30-60	45-55
5	glycerin	5-20	7.5-15	10-12.5
	flavors	1-10	2-8	3-6

C. Ciprofloxacin hydrochloride bite capsule

		Amounts	preferred amount	most preferred amount
10	Ciprofloxacin hydrochloride	25-65	35-55	40-50
	glycerin	5-20	7.5-15	10-12.5
	polyethylene glycol	20-75	30-65	40-60
	flavors	1-10	2-8	3-6

15 D. zidovudine (formerly called azidothymidine (AZT) (Retrovir) lingual spray

		Amounts	preferred amount	most preferred amount
	zidovudine	10-50	15-40	25-35
	water	30-80	40-75	45-70
	ethanol	5-20	7.5-15	9.5-12.5
20	polyethylene glycol	5-20	7.5-15	9.5-12.5
	flavors	0.1-5	1-4	2-3

## EXAMPLE 5

## Anti-emetics

25 A. Ondansetron hydrochloride lingual spray

		Amounts	preferred amount	most preferred amount
	ondansetron hydrochloride	1-25	2-20	2.5-15
	citric acid monohydrate,	1-10	2-8	2.5-5
	sodium citrate dihydrate	0.5-5	1-4	1.25-2.5
30	water	1-90	5-85	10-75
	ethanol	5-30	7.5-20	9.5-15
	propylene glycol	5-30	7.5-20	9.5-15
	polyethylene glycol	5-30	7.5-20	9.5-15
	flavors	1-10	3-8	5-7.5

B. Dimenhydrinate bite capsule

		Amounts	preferred amount	most preferred amount
	Dimenhydrinate	0.5-30	2-25	3-15
	glycerin	5-20	7.5-15	10-12.5
5	polyethylene glycol	45-95	50-90	55-85
	flavors	1-10	2-8	3-6

C. Dimenhydrinate polar lingual spray

		Amounts	preferred	most preferred
			amount	amount
10	Dimenhydrinate	3-50	4-40	5-35
	water	5-90	10-80	15-75
	ethanol	1-80	3-50	5-10
	polyethylene	1-80	3-50	5-15
	glycol			
15	Sorbitol	0.1-5	0.2-4	0.4-1.0
	aspartame	0.01-0.5	0.02-0.4	0.04-0.1
	flavors	0.1-5	1-4	2-3

## EXAMPLE 6

## 20 Histamine H-2 receptor antagonists

A. Cimetidine hydrochloride bite capsule

		Amounts	preferred amount	most preferred amount
	Cimetidine Hcl	10-60	15-55	25-50
	glycerin	5-20	7.5-15	10-12.5
25	polyethylene glycol	20-90	25-85	30-75
	flavors	1-10	2-8	3-6

B. Famotidine lingual spray

		Amounts	preferred amount	most preferred amount
30	Famotidine	1-35	5-30	7-20
	water	2.5-25	3-20	5-10
	L-aspartic acid	0.1-20	1-15	5-10
	polyethylene glycol	20-97	30-95	50-85
	flavors	0.1-10	1-7.5	2-5

C. Famotidine non-polar lingual spray

	Amounts	preferred amount	most preferred amount
	Famotidine	1-35	5-30
	Soya oil	10-50	15-40
5	Butane	✓15-80	30-75
	polyoxyethyl- ated oleic glycerides	10-50	15-40
	flavors	0.1-5	1-4
10			2-3

## EXAMPLE 7

## Barbiturates

A. Phenytoin sodium lingual spray

	Amounts	preferred amount	most preferred amount
15	Phenytoin sodium	10-60	15-55
	water	2.5-25	3-20
	ethanol	5-30	7.5-20
	propylene glycol	5-30	7.5-20
	polyethylene glycol	5-30	7.5-20
20	flavors	1-10	3-8
			5-7.5

B. Phenytoin non-polar lingual spray

	Amounts	preferred amount	most preferred amount
	Phenytoin	5-45	10-40
25	miglyol	10-50	15-40
	Butane	✓ 15-80	30-75
	polyoxyethyl- ated oleic glycerides	10-50	15-40
30	flavors	0.1-10	1-8
			5-7.5

## EXAMPLE 8

## Prostaglandins

A. Carboprost thromethamine lingual spray

		Amounts	preferred amount	most preferred amount
5	Carboprost thromethamine	0.05-5	0.1-3	0.25-2.5
	water	50-95	60-80	65-75
	ethanol	5-20	7.5-15	9.5-12.5
	polyethylene glycol	5-20	7.5-15	9.5-12.5
	sodium chloride	1-20	3-15	4-8
10	flavors	0.1-5	1-4	2-3

Ph is adjusted with sodium hydroxide and/or hydrochloric acid

B. Carboprost non-polar lingual spray

		Amounts	preferred amount	most preferred amount
15	Carboprost	0.05-5	0.1-3	0.25-2.5
	miglyol	25-50	30-45	35-40
	Butane	5-60	10-50	20-35
	polyoxyethyl- ated oleic	25-50	30-45	35-40
20	glycerides			
	flavors	0.1-10	1-8	5-7.5

## EXAMPLE 9

## Neutraceuticals

25 A. Carnitine as bite capsule (contents are a paste)

		Amounts	preferred amount	most preferred amount
	Carnitine fumarate	6-80	30-70	45-65
	soya oil	7.5-50	10-40	12.5-35
	soya lecithin	0.001-1.0	0.005-0.5	.01-0.1
30	Soya fats	7.5-50	10-40	12.5-35
	flavors	1-10	2-8	3-6

B. Valerian as lingual spray

	Amounts	preferred amount	most preferred amount
Valerian extract	0.1-10	0.2-7	0.25-5
water	50-95	60-80	65-75
5 ethanol	5-20	7.5-15	9.5-12.5
polyethylene glycol	5-20	7.5-15	9.5-12.5
flavors	1-10	2-8	3-6

B. Echinacea as bite capsule

	Amounts	preferred amount	most preferred amount
Echinacea extract	30-85	40-75	45-55
soya oil	7.5-50	10-40	12.5-35
soya lecithin	0.001-1.0	0.005-0.5	.01-0.1
Soya fats	7.5-50	10-40	12.5-35
15 flavors	1-10	2-8	3-6

B. Mixtures of ingredients

	Amounts	preferred amount	most preferred amount
Magnesium oxide	15-40	20-35	25-30
20 Chromium picolinate	0.01-1.0	0.02-0.5	.025-0.75
folic acid	.025-3.0	0.05-2.0	0.25-0.5
vitamin B-12	0.01-1.0	0.02-0.5	.025-0.75
vitamin E	15-40	20-35	25-30
Soya oil	10-40	12.5-35	15-20
25 soya lecithin	0.1-5	0.2-4	0.5-1.5
soya fat	10-40	15-35	17.5-20

## EXAMPLE 10

## Sleep Inducers (also CNS active amine)

A. Diphenhydramine hydrochloride lingual spray

		Amounts	preferred amount	most preferred amount
5	Diphenhydramine	3-50	4-40	5-35
	Hcl			
	water	5-90	10-80	50-75
	ethanol	1-80	3-50	5-10
	polyethylene	1-80	3-50	5-15
10	glycol			
	Sorbitol	0.1-5	0.2-4	0.4-1.0
	aspartame	0.01-0.5	0.02-0.4	0.04-0.1
	flavors	0.1-5	1-4	2-3

15

## EXAMPLE 11

## Anti-Asthmatics-Bronchodilators

A. Isoproterenol Hydrochloride as polar lingual spray

		Amounts	preferred amount	most preferred amount
	Isoproterenol	0.1-10	0.2-7.5	0.5-6
20	Hydrochloride			
	water	5-90	10-80	50-75
	ethanol	1-80	3-50	5-10
	polyethylene	1-80	3-50	5-15
	glycol			
25	Sorbitol	0.1-5	0.2-4	0.4-1.0
	aspartame	0.01-0.5	0.02-0.4	0.04-0.1
	flavors	0.1-5	1-4	2-3

B. Terbutaline sulfate as polar lingual spray

	Amounts	preferred amount	most preferred amount
Terbutaline sulfate	0.1-10	0.2-7.5	0.5-6
5 water	5-90	10-80	50-75
ethanol	1-10	2-8	2.5-5
Sorbitol	0.1-5	0.2-4	0.4-1.0
aspartame	0.01-0.5	0.02-0.4	0.04-0.1
flavors	0.1-5	1-4	2-3

10

C. Terbutaline as non-polar lingual spray

	Amounts	preferred amount	most preferred amount
Terbutaline	0.1-10	0.2-7.5	0.5-6
miglyol	25-50	30-45	35-40
15 isobutane	5-60	10-50	20-35
polyoxyethylated oleic glycerides	25-50	30-45	35-40
flavors	0.1-10	1-8	5-7.5

20

D. Theophylline polar bite capsule

	Amounts	preferred amount	most preferred amount
Theophylline	5-50	10-40	15-30
polyethylene glycol	20-60	25-50	30-40
25 glycerin	25-50	35-45	30-40
propylene glycol	25-50	35-45	30-40
flavors	0.1-5	1-4	2-3

E. Albuterol sulfate as polar lingual spray

	Amounts	preferred amount	most preferred amount
	Albuterol sulfate	0.1-10	0.2-7.5
	water	5-90	10-80
5	ethanol	1-10	2-8
	Sorbitol	0.1-5	0.2-4
	aspartame	0.01-0.5	0.02-0.4
	flavors	0.1-5	1-4
			2-3

## WHAT IS CLAIMED IS:

1. A buccal aerosol spray composition for transmucosal administration of a pharmacologically active compound  
5 provided that where the said active compound is soluble in a pharmacologically acceptable polar solvent said composition comprises in weight % of total composition: aqueous polar solvent 30-99.69%, active compound 0.001-60%,  
and where said active compound is soluble in a pharmacologically acceptable non-polar solvent said composition comprises in weight % of total composition: pharmaceutically acceptable propellant selected from the group consisting of  $C_{3-8}$  hydrocarbon of a linear or branched configuration 50-80% non-polar solvent 20-85%, active compound 0.05-50%,  
wherein the active compound is selected from the group consisting of biologically active peptides, central nervous system active amines, sulfonyl ureas, antibiotics, antifungals, antivirals, sleep inducers, antiasthmatics, bronchial dilators, antiemetics, histamine H-2 receptor antagonists, barbiturates, prostoglandins, anti-asthmatics, bronchial dilators and neutraceuticals.

20

2. The composition of claim 1 additionally comprising, by weight of total composition: flavoring agent 0.1-10%.

3. The composition of claim 1 comprising: polar solvent 37-25 98.58%, active compound 0.0005-55%, flavoring agent 0.5-8%.

4. The composition of claim 1 comprising: polar solvent 60.9-97.06%, active compound 0.01-40%, flavoring agent 0.75-7.5%.

- 30 5. The composition of Claim 1 wherein the polar solvent is selected from the group consisting of low molecular weight polyethylene-

glycols (PEG) of 400-1000 MW, C<sub>2</sub>-C<sub>8</sub> mono- and poly-alcohols, and alcohols of C<sub>7</sub>-C<sub>18</sub> hydrocarbons of a linear or branched configuration.

6. The composition of Claim 1 wherein the solvent is aqueous 5 ethylene glycol.

7. The composition of Claim 1 wherein the solvent is aqueous ethanol.

10 8. The composition of Claim 1 wherein the active compound is selected from the group consisting of cyclosporin, clozapine, zidevudine, erythromycin, odansetron, cimetidine, phenytoin, carboprost thromethamine, valerian and isoproterenol in their nonionized form or as the pharmaceutically acceptable salts thereof.

15

9. The composition of Claim 2 wherein the flavoring agents are selected from the group consisting of synthetic or natural oil of peppermint, oil of spearmint, citrus oil, fruit flavors, sweeteners and combinations thereof.

20

10. The composition of Claim 2 of the formulation: polar solvent 75-85%, cyclosporin 15-25%, flavoring agent 0.1-5%.

11. The composition of Claim 2 of the formulation: polar solvent 25 75-84%, odansitron hydrochloride 2.5-15%, flavoring agent 1-10%.

12. A method of administering a pharmacologically active compound to a mammal in need of same, by spraying the oral mucosa of said mammal with a composition of claim 1.

30

13. The method of claim 12 wherein the amount of spray administered is predetermined.

14. The composition of claim 1 comprising: propellant 10-25%,  
5 non-polar solvent 25-89.95%, active compound 0.1-40%, flavoring agent 1-8%.

15. The composition of claim 1 comprising: propellant 20-70%,  
non-polar solvent 30-74.75%, active compound 0.25-35%, flavoring agent  
10 2-7.5%.

16. The composition of Claim 1 wherein the propellant is propane, N-butane, iso-butane, N-pentane, iso-pentane, or neo-pentane, and mixtures thereof.

15

17. The composition of Claim 1 wherein the propellant is n-butane or iso-butane and has a water content of no more than 0.2% and oxidizing agents, reducing agents, and Lewis acids or bases content in a concentration of less than 0.1%.

20

18. The composition of Claim 1 wherein the solvent is a selected from the group consisting of (C<sub>2</sub>-C<sub>24</sub>) fatty acid (C<sub>2</sub>-C<sub>6</sub>) esters, C<sub>7</sub>-C<sub>18</sub> hydrocarbons of a linear or branched configuration, and C<sub>2</sub>-C<sub>6</sub> alkanoyl esters, and triglycerides of the corresponding acids.

25

19. The composition of Claim 1 wherein the solvent is miglyol.

20. The composition of Claim 1 of the formulation: propellant 15-80%, non-polar solvent 20-85%, clozepine 0.5-30%, flavoring agent  
30 1-5%.

21. The composition of Claim 1 of the formulation: propellant 15-80%, non-polar solvent 20-85%, zidovudine 25-35%, flavoring agent 0.1-5%.

5 22. The composition of Claim 1 of the formulation: propellant 5-60%, non-polar solvent 15-98.5%, carboprost 0.05-5%, flavoring agent 0.1-10%.

10 23. The composition of Claim 1 of the formulation: propellant 5-60%, non-polar solvent 20-94.8%, terbutaline 0.5-6%, flavoring agent 0.01-10%.

15 24. A soft bite gelatin capsule for transmucosal administration of a pharmacologically active compound, where said active compound is at least partially soluble in a pharmacologically acceptable polar solvent, having charged thereto a fill composition comprising in weight % of total fill composition: polar solvent 25-99.89%, emulsifier 0-20%, active compound 0.01-65%,  
and where said active compound is at least partially soluble in a pharmacologically acceptable non-polar solvent, having charged thereto a fill composition comprising in weight % of total fill composition: non-polar solvent 4-99.99%, emulsifier 0-20%, active compound 0.01-80%,  
wherein the active compound is selected from the group consisting of biologically active peptides, central nervous system active amines, sulfonyl ureas, antibiotics, antifungals, antivirals, sleep inducers, antiasthmatics, bronchial dilators, antiemetics, histamine H-2 receptor antagonists, barbiturates, prostoglandins and neutraceuticals, provided that said composition contains less than 10% of water.

25. The composition of Claim 24 wherein the active compound is selected from the group consisting of cyclosporin, clozapine, glyburide, erythromycin, odansetron, cimetidine, phenytoin, carboprost thromethamine and valerian in their nonionized form or as the pharmaceutically acceptable  
5 salts thereof.

26. The capsule of Claim 24 wherein the active compound is in their nonionized form or as the free base of the pharmaceutically acceptable salts thereof.

10

27. The capsule of Claim 24 wherein the flavoring agents are synthetic or natural oil of peppermint, oil of spearmint, citrus oil, fruit flavors, or sweeteners and combinations thereof.

15

28. The capsule of claim 24 additionally comprising, by weight of the fill composition: flavoring agent 0.1-10%.

20

29. The soft bite gelatin capsule of Claim 24 comprising as the fill composition: polar solvent 37-98.95%, emulsifier 0-15%, active compound 0.025-55%, flavoring agent 1-8%.

25

30. The soft bite gelatin capsule of Claim 24 comprising as the fill composition: polar solvent 44-96.925%, emulsifier 0-10%, active compound 0.075-50%, flavoring agent 2-6%.

30

31. The capsule of Claim 24 wherein the solvent is selected from the group consisting of low molecular weight polyethyleneglycols (PEG) of 400-1000 MW, C<sub>2</sub>-C<sub>8</sub> mono- and poly-alc hols, and alcohols of C<sub>7</sub>-C<sub>18</sub> hydrocarbons of a linear or branch d configuration.

32. The capsule of Claim 24 wherein the solvent is selected from low molecular weight polyethyleneglycols (PEG) of 400-600 MW.

33. The capsule of Claim 24 comprising: non-polar solvent 21.5-5 99.975%, emulsifier 0-15%, active compound 0.025-70%, flavoring agent 1-8%.

34. The capsule of Claim 24 comprising: non-polar solvent 28.5-97.9%, emulsifier 0-10%, active compound 0.1-65%, flavoring agent 10 2-6%.

35. The capsule of Claim 24 wherein the solvent is selected from the group consisting of (C<sub>2</sub>-C<sub>24</sub>) fatty acid (C<sub>2</sub>-C<sub>6</sub>) esters, C<sub>7</sub>-C<sub>18</sub> hydrocarbons of a linear or branched configuration, and C<sub>2</sub>-C<sub>6</sub> alkanoyl esters, and 15 triglycerides of the corresponding acids.

36. The capsule of Claim 24 comprising as the fill composition the formulation: polar solvent 75-99%, emulsifier 0-20%, cyclosporine 15-25%, flavoring agent 0.1-6%.

20

37. The capsule of Claim 24 comprising as the fill composition the formulation: polar solvent 25-99.89%, emulsifier 0-20%, sumatriptan succinate 0.01-5%, flavoring agent 0.1-10%.

25 38. The capsule of Claim 24 comprising as the fill composition the formulation: polar solvent 30-89%, emulsifier 0-20%, cimetidine hydrochloride 10-60%, flavoring agent 1-10%.

39. The capsule of Claim 24 comprising as the fill composition the 30 formulation: polar solvent 60-98.5%, emulsifier 0-20%, dimenhydrinate 0.5-30%, flavoring agent 1-10%.

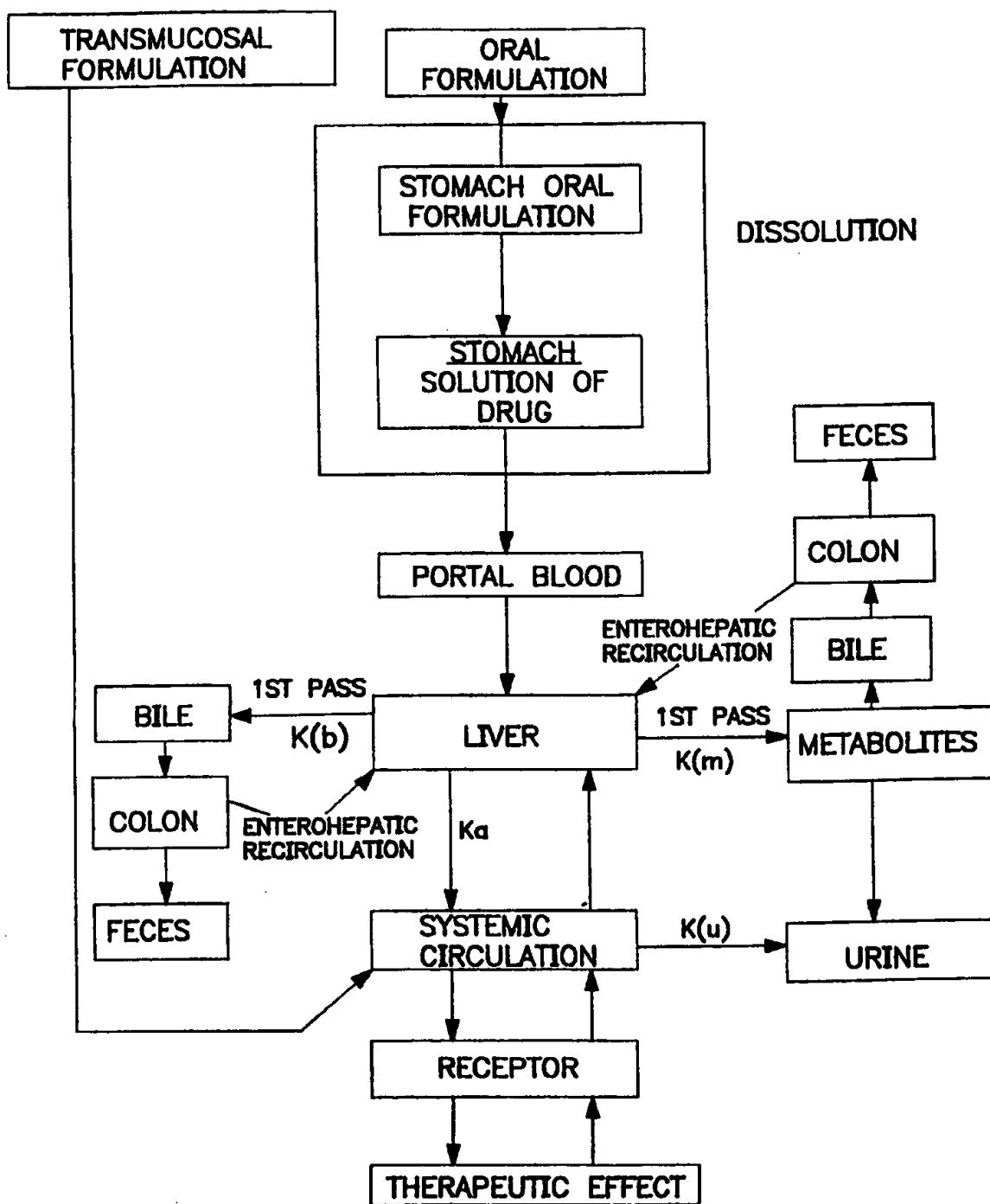
40. The capsule of Claim 24 comprising as the fill composition the formulation: polar solvent 45-94.9%, emulsifier 0-20%, theophylline 5.0-50%, flavoring agent 0.5-5%.

5 41. The capsule of Claim 24 comprising as the fill composition the formulation: polar solvent 7.5-99.8%, emulsifier 0-20%, carnitine fumarate 6-80%, flavoring agent 1-10%.

42. A buccal pump spray composition for transmucosal administration of a pharmacologically active compound where said active compound is soluble in a pharmacologically acceptable non-polar solvent said composition comprises in weight % of total composition: non-polar solvent 30-99.69%, active compound 0.005-55%, flavoring agent 0.1-10%, wherein the active compound is selected from the group consisting of biologically active peptides, central nervous system active amines, sulfonyl ureas, antibiotics, antifungals, antivirals, sleep inducers, antiasthmatics, bronchial dilators, antiemetics, histamine H-2 receptor antagonists, barbiturates, prostoglandins and neutraceuticals.

20 43. A buccal pump spray composition for transmucosal administration of a pharmacologically active compound where said active compound is soluble in a pharmacologically acceptable non-polar solvent said composition comprises in weight % of total composition: non-polar solvent 30-99.69%, active compound 0.005-55%, flavoring agent 0.1-10%, wherein the active compound is selected from the group consisting of antihistamines, alkaloids, hormones, benzodiazepines and narcotic analgesics.

1 / 1



$$K(\ ) = K_m + K(b) + K(u)$$

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/17899

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 633 933 A (EGIS GYOGYSZERGYAR) 12 January 1990 see claims 1-10 see examples 1-7 ---	1-7, 9, 12, 13
X	DE 33 38 978 A (BASF) 3 May 1984  see claims 2,3 see page 8, line 12 - line 24 see page 12; examples 3,4 ---	1-5, 7, 9, 12, 13, 24, 26-32
X	EP 0 471 161 A (SCHWARZ PHARMA) 19 February 1992 see claims 1-6 ---	1-5, 7, 12, 13 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

1 February 1999

Date of mailing of the international search report

10.02.1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo rd.  
Fax: (+31-70) 340-3016

Authorized officer

Ventura Amat, A

**INTERNATIONAL SEARCH REPORT**

International Application No

PCT/US 97/17899

**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 40 38 203 A (KALI-CHEMIE PHARMA) 4 June 1992  see claims 1-6 see table 1 ---	1,2,9, 12-15, 18,19
X	DE 32 46 081 A (G. POHL-BOSKAMP) 14 June 1984  see example 1 see page 4, line 5 - line 21 see page 3, line 12 - line 33 see claim 1 ---	1,2,9, 12-15, 18,19
X	EP 0 656 206 A (SCHERING CORPORATION) 7 June 1995  see example 2 see page 3, line 11 - page 6, line 30 see claims 1,2,4,8 ---	1,2,8,9, 12-15, 18,19,23
X	US 4 935 243 A (LIONEL BORKAN, ET AL.) 19 June 1990  see examples 1,2 see claims 1-8 ---	24, 26-28, 33-35
X	DE 40 07 705 C (G. POHL-BOSKAMP) 26 September 1991 see claim 1 ---	42
E	WO 97 38663 A (FLEMINGTON PHARMACEUTICAL CORPORATION) 23 October 1997  see claims 1-36 ---	1,2,9, 12-19, 24, 26-28, 33-35
E	WO 97 38687 A (FLEMINGTON PHARMACEUTICAL) 23 October 1997 see claims 1-15 ---	1,2,9, 12-19
A	WO 95 24893 A (R. P. SCHERER) 21 September 1995 see the whole document ---	1-43
		-/-

**INTERNATIONAL SEARCH REPORT**

Inte onal Application No

PCT/US 97/17899

**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 90 01046 A (ZILA PHARMACEUTICALS)  8 February 1990  see examples 1,6  see page 9, paragraph 4 – page 10,  paragraph 1  see page 8, paragraph 4 – page 9,  paragraph 1  see page 6, line 1 – line 5  see page 4, paragraph 3 – page 5,  paragraph 1  -----</p>	1,7,8, 12,13

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

PCT/US 97/17899

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
FR 2633933	A 12-01-1990	AT 401613 B AT 165489 A BE 1003253 A CH 679371 A CY 1761 A DE 3922650 A GB 2220949 A, B HU 9500271 A JP 1925324 C JP 2142726 A JP 6051620 B NL 8901751 A SU 1837871 A US 5047230 A		25-10-1996 15-03-1996 11-02-1992 14-02-1992 15-07-1994 11-01-1990 24-01-1990 28-09-1995 25-04-1995 31-05-1990 06-07-1994 01-02-1990 30-08-1993 10-09-1991
DE 3338978	A 03-05-1984	NONE		
EP 471161	A 19-02-1992	DE 4026072 A AT 110567 T BG 60852 B CS 9102099 A DK 471161 T ES 2060248 T FI 913882 A HR 920988 A IE 65273 B JP 2111686 C JP 4230627 A JP 8018981 B PT 98658 A SI 9111215 A SK 279132 B RU 2060733 C US 5744124 A		20-02-1992 15-09-1994 31-05-1996 19-02-1992 03-10-1994 16-11-1994 18-02-1992 31-10-1996 18-10-1995 21-11-1996 19-08-1992 28-02-1996 30-06-1992 31-08-1995 08-07-1998 27-05-1996 28-04-1998
DE 4038203	A 04-06-1992	NONE		
DE 3246081	A 14-06-1984	NONE		
EP 656206	A 07-06-1995	EP 0656207 A AT 134509 T AU 2017592 A CA 2111002 A CN 1067578 A CZ 9302714 A DE 69208660 D DE 69208660 T DK 588897 T EP 0518600 A EP 0588897 A ES 2084360 T FI 935464 A GR 3019374 T HK 185596 A HU 67449 A JP 6511235 T MX 9202750 A NO 934500 A		07-06-1995 15-03-1996 12-01-1993 23-12-1992 06-01-1993 13-07-1994 04-04-1996 11-07-1996 18-03-1996 16-12-1992 30-03-1994 01-05-1996 07-12-1993 30-06-1996 11-10-1996 28-04-1995 15-12-1994 31-12-1992 09-12-1993

**INTERNATIONAL SEARCH REPORT**

Information on patent family members				International Application No PCT/US 97/17899
Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 656206 A		OA 9868 A SK 140493 A WO 9222288 A US 5474759 A		15-08-1994 05-10-1994 23-12-1992 12-12-1995
US 4935243 A	19-06-1990	AU 616139 B AU 3811089 A CA 1336499 A EP 0374359 A JP 2212417 A MX 166393 B		17-10-1991 21-06-1990 01-08-1995 27-06-1990 23-08-1990 06-01-1993
DE 4007705 C	26-09-1991	AT 125703 T CA 2037487 C DE 59106106 D DK 448961 T EP 0448961 A ES 2075908 T GR 3017032 T IE 68451 B US 5186925 A		15-08-1995 18-04-1995 07-09-1995 11-12-1995 02-10-1991 16-10-1995 30-11-1995 26-06-1996 16-02-1993
WO 9738663 A	23-10-1997	AU 2190797 A		07-11-1997
WO 9738687 A	23-10-1997	AU 1969397 A		07-11-1997
WO 9524893 A	21-09-1995	AU 686767 B AU 1897495 A CA 2185347 A EP 0750495 A JP 10503750 T US 5645856 A		12-02-1998 03-10-1995 21-09-1995 02-01-1997 07-04-1998 08-07-1997
WO 9001046 A	08-02-1990	AU 2252388 A CA 1337396 A EP 0380647 A KR 9411240 B MX 21686 A NO 180618 B WO 8910745 A US 5081158 A US 5081157 A		29-11-1989 24-10-1995 08-08-1990 03-12-1994 31-01-1994 10-02-1997 16-11-1989 14-01-1992 14-01-1992